RE: EFFICACY AND SAFETY OF PAXIL CR® FOR MAJOR DEPRESSIVE DISORDER

SUMMARY

- The efficacy and safety of Paxil CR® (paroxetine HCl) Controlled-Release for major depressive disorder (MDD) has been evaluted in several flexible-dose and fixed-dose clinical trials in adult and elderly patients.
- Common adverse events reported with *Paxil CR* in a pool of 2 adult trials for MDD (≥5% and at least twice that for placebo) included: sweating, abnormal vision, constipation, somnolence, decreased appetite, infection, dry mouth, decreased libido, diarrhea, dizziness, female genital disorders, nausea, impotence, abnormal ejaculation, trauma, tremor, and yawning.

Some information contained in this response may be outside the approved Prescribing Information for *Paxil CR*. This response is not intended to offer recommendations for administering *Paxil CR* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Paxil CR*, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Paxil CR*.

CLINICAL TRIALS

Adult Flexible-Dose Trials

Two identical 12-week, multicenter, placebo-controlled flexible-dose trials in adult patients aged 18-65 years have been conducted to evaluate the efficacy and safety of *Paxil CR* in the treatment of MDD (1). These studies enrolled patients with MDD (DSM-IV criteria) and a Hamilton Rating Scale for Depression (HAM-D) score ≥20 (2, 3). The HAM-D evaluates both the emotional and physical symptoms of depression. Patients with another Axis I disorder within the previous 6 months or history of a seizure disorder were excluded. Patients were also excluded based upon a history of alcohol or drug abuse within the previous 6 months, electroconvulsive therapy (ECT) within the previous 3 months, or if they were presently receiving psychotherapy. Patients taking monoamine oxidase inhibitors (MAOIs), benzodiazepines, and other psychoactive medications, other than chloral hydrate were excluded. In addition, patients taking warfarin, phenytoin, cimetidine, sumatriptan, type 1C antiarrhythmics, quinidine, or sulfonylurea derivatives were also excluded.

The primary efficacy parameter was the change from baseline to study endpoint on the HAM-D total score (2). Secondary efficacy parameters included HAM-D depressed mood item score, HAM-D sleep disturbance score, HAM-D anxiety factor score, and the Clinical Global Impression -Severity of Illness score (CGI-S). Therapeutic response, defined as a Clinical Global Impression-Improvement score (CGI-I) of 1 (very much improved) or 2 (much improved), was assessed. In addition, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), overall life satisfaction, and medication satisfaction in the Q-LES-Q was assessed. Safety was evaluated through routine adverse experience monitoring. These studies included a Paxil® (paroxetine HCl) treatment arm; however, they were not designed to compare the efficacy of *Paxil* to *Paxil CR*. The efficacy of *Paxil CR* was established based on a comparison with placebo.

Various types of data analyses were performed. For the last observation carried forward (LOCF) analysis, the last observation on treatment was carried forward to estimate missing data. LOCF is the most conservative analysis. The observed cases (OC) population consisted of patients who had available data at each week of the study and reflect patients who completed therapy. The random-effects mixed

modeling (REMM) analysis, which accounts for the longitudinal nature of clinical trial design, utilizes all available data regardless of patient dropouts to estimate a growth curve for each treatment arm. The REMM approach can be applied to continuous measures used in longitudinal research. It accounts for the repeated measures, and models the overall change in scores seen in all patients. No data are extrapolated from earlier time points, like in LOCF analyses. The benefit of REMM is that it allows for random patient dropouts and models what those patients' treatment responses would look like had they remained in the trial. This analysis was included to provide a more sensitive and accurate estimation of overall symptom improvement for each group.

A total of 640 patients, aged 18 to 65 years, were enrolled in the 2 adult flexible-dose clinical trials (2, 3). For both clinical trials combined, the mean age of patients was 40.2 years; 65% of patients were women. Patient demographics were similar among groups within the individual studies. For both trials combined, the mean baseline total HAM-D score was 23.5. Patients were randomized to flexible treatment with *Paxil CR* 25 mg to 62.5 mg, *Paxil* 20 mg to 50 mg, or placebo in a 1:1:1 ratio. Patients were initiated with *Paxil CR* 25 mg or *Paxil* 20 mg and could be titrated at weekly intervals by 12.5 mg and 10 mg, respectively.

Individual Study Results - Flexible-Dose Trials

In study 1, the mean change from baseline in total HAM-D (LOCF) among patients taking *Paxil CR* (n = 108) was significantly better than among those assigned to placebo (n = 110) (2, 3). In addition, *Paxil CR* was significantly better than placebo at endpoint (week 12) on the HAM-D depressed mood item score, HAM-D anxiety factor score, and the CGI-S score (Table 1). At study endpoint, patients taking *Paxil CR* had significantly better scores on all sections of the Q-LES-Q compared with placebo-treated patients ($P < 0.001$).

Table 1. Efficacy Results of Study 1 at Endpoint (3)

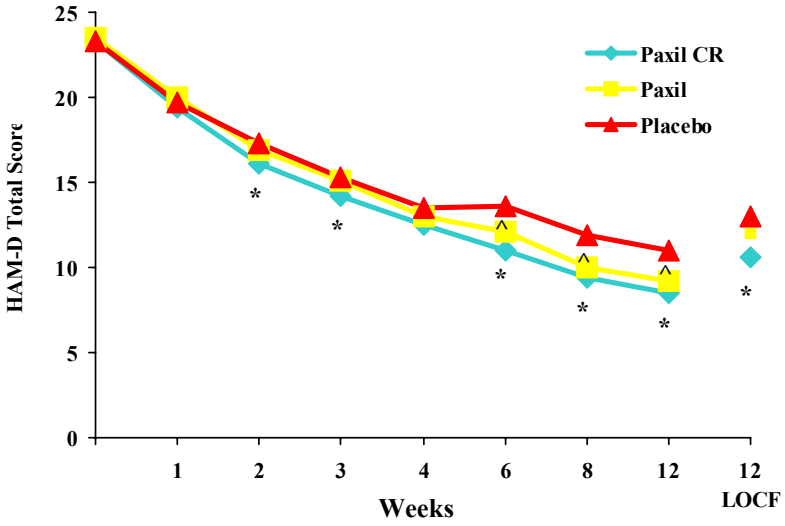
Mean Change from Baseline LOCF	**Placebo n = 110**	***Paxil CR* n = 108**
HAM-D Total Score	-10.2	-13.3*
HAM-D Depressed Mood Item	-0.8	-1.3*
HAM-D Anxiety Factor	-2.9	-3.8*
HAM-D Sleep Factor	-1.0	-1.4
Responder: CGI-I Score 1 or 2	50.5%	64.6%*
*$P < 0.05$ versus placebo CGI-I = Clinical Global Impression-Improvement score; HAM-D = Hamilton Depression Rating Scale; LOCF = last observation carried forward		

In the second study, overall results supported the efficacy of *Paxil CR*. However, due to a treatment by center interaction, 1 center (18 patients) was excluded from all analyses of many of the efficacy parameters (2, 3). This center had a treatment by site interaction that favored *Paxil CR* and *Paxil* over placebo, with efficacy of 100% with either active treatment and 0% with placebo. This center was excluded, and the results of the primary endpoint, change in total HAM-D score, did not reach statistical significance compared to placebo. Overall, this study reported fewer statistically significant results compared to placebo, however, *Paxil CR* (n = 94) was significantly better than placebo (n = 93) at endpoint (week 12) on the HAM-D depressed mood item score. Therapeutic response, defined as a CGI-I score of 1 or 2, was reported in 67.6% and 49.5% of patients treated with *Paxil CR* and placebo, respectively ($P < 0.05$) (LOCF). In addition, patients receiving *Paxil CR* had significant improvements on several sections of the Q-LES-Q compared with those receiving placebo.

Combined Analyses - Flexible-Dose Trials

The 2 adult trials, identical in design, were pooled for several analyses to improve statistical power by increasing the number of patients in the pooled data set. The mean change from baseline to endpoint in the HAM-D total score (LOCF and OC) among patients taking *Paxil CR* and *Paxil* was significantly better than among those assigned to placebo (Figure 1) (2, 4). In addition, *Paxil CR* was significantly better than placebo at endpoint on the HAM-D depressed mood item score (Table 2) and the HAM-D anxiety factor score (Figure 2) (2, 4).

Figure 1. HAM-D Total Score for Adult Flexible-Dose Studies (2, 4)



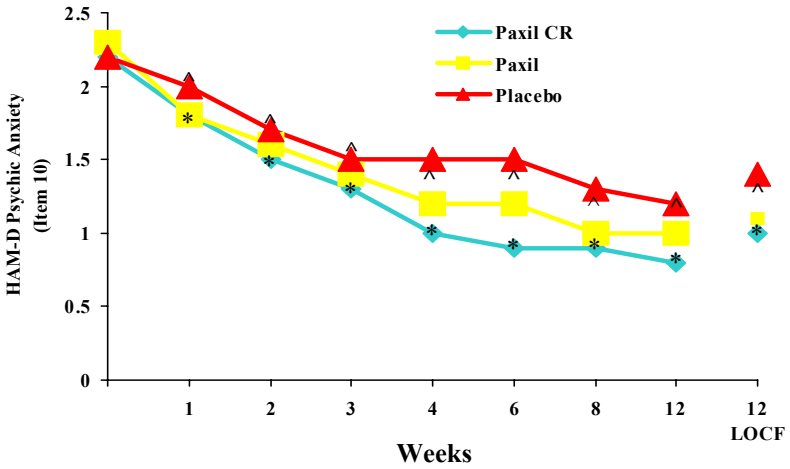
*$P < 0.05$ *Paxil CR* vs. placebo, ^$P < 0.05$ *Paxil* vs. placebo,
LOCF= last observation carried forward

Table 2. Combined Efficacy Results of Adult Flexible-Dose Studies at Endpoint (2, 3)

Mean Change from Baseline LOCF	***Paxil CR* n = 204**	***Paxil* n = 208**	**Placebo n = 205**
HAM-D Depressed Mood Item	-1.7*	-1.6*	-1.2
Responder: HAM-D ≥50% reduction	59.8%*	55.8%	48.3%
Remission: HAM-D ≤7	44.6%*	37.0%	33.7%
Mean Change from Baseline OC	***Paxil CR* n = 137**	***Paxil* n = 118**	**Placebo n = 134**
HAM-D Depressed Mood Item	-1.9*	-2.0*	-1.5
Responder: HAM-D ≥50% reduction	73.7%*	72.9%*	61.2%
Remission: HAM-D ≤7	56.2%*	52.5%	44.0%

* $P < 0.05$ active treatment versus placebo
HAM-D = Hamilton Depression Rating Scale; LOCF = last observation carried forward, OC = observed cases

Figure 2. HAM-D Psychological Anxiety for Adult Flexible-Dose Studies (2)



*P < 0.05 CR vs. placebo, ^P < 0.05 *Paxil* vs. placebo
LOCF = last observation carried forward

At week 12, patients receiving *Paxil CR* had statistically significant improvements in response (≥50% reduction in HAM-D) compared to placebo. Patient response was 73.7% for *Paxil CR,* 73% for *Paxil*, and 61.2% for placebo (P ≤0.05 vs placebo).

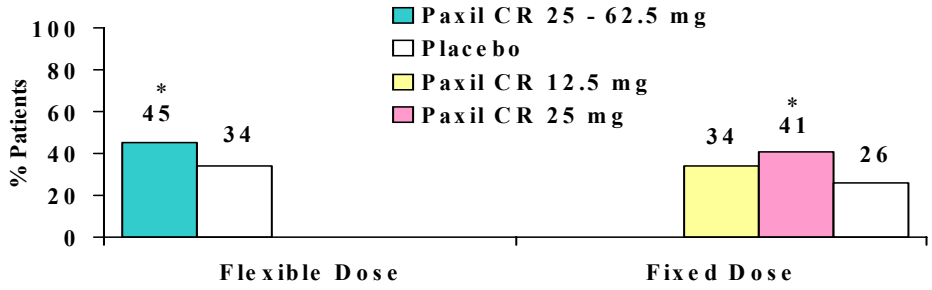
In addition, patients treated with *Paxil CR* noted improvements in various sections on the Q-LES-Q (4). Finally, additional analyses of the HAM-D scores were conducted using REMM. With this analysis, an overall difference over time for the HAM-D total score at endpoint was observed with *Paxil CR* (mean score 8.8, P = 0.0003) and *Paxil* (mean score 9.5, P = 0.036), respectively, compared to placebo (2, 4). Moreover, REMM evaluation of depressed mood item and anxiety factor score revealed significant improvements for *Paxil CR* and *Paxil* compared to placebo.

Common adverse events reported with the use of *Paxil CR* from the pooled analysis of 2 flexible-dose adult trials for MDD (≥5% and at least twice that for placebo) included: sweating, abnormal vision, constipation, somnolence, decreased libido, diarrhea, dizziness, female genital disorders, nausea, abnormal ejaculation, trauma, tremor, and yawning (1). Dropout rates due to adverse events in the pooled analysis were 10% for *Paxil CR*, 16% for *Paxil*, and 6% for placebo (2).

Remission Analyses – Flexible-Dose Trials

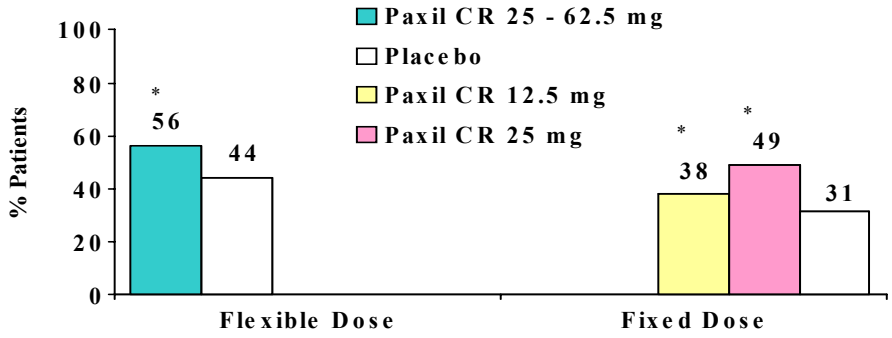
By week 3 in the 2 pooled adult trials, a greater proportion of patients receiving *Paxil CR* achieved remission compared with placebo, LOCF and OC (P < 0.05) (2, 4). After 6 weeks of treatment, remission rates were 34.4% for *Paxil CR* compared with 20.5% for placebo (OC). At week 12, patients receiving *Paxil CR* had statistically significant improvements in remission (HAM-D ≤7) rates compared with placebo for both LOCF and OC analyses (Figures 3-4).

Figure 3. Remission Data for *Paxil CR* in Adult Trials, LOCF (2, 4)



Remission defined as HAM-D ≤7
* $P < 0.05$ vs placebo

Figure 4. Remission Data for *Paxil CR* in Adult Trials, OC (2, 4)



Remission defined as HAM-D ≤7
* $P < 0.05$ vs placebo

Elderly Trials

A total of 323 patients aged 60 to 88 years diagnosed with MDD received treatment with flexible doses of *Paxil CR* 12.5 to 50 mg/day or *Paxil* 10 to 40 mg/day (5, 6, 7). Treatment groups were similar with respect to age (mean age 70 years in the treatment groups and 69 years in the placebo group), patient demographics and baseline characteristics. The mean baseline total HAM-D scores were 22.1, 22.3, and 22.1 for *Paxil CR*, *Paxil* and placebo, respectively. Patients were randomized to *Paxil CR* (n = 104), *Paxil* (n = 106), or placebo (n = 109). Therapy was initiated at the lower dosage level (*Paxil CR* 12.5 mg/day or *Paxil* 10 mg/day). Dosage elevations were permitted, at the discretion of the investigator, according to clinical response and tolerability to a maximum dose of *Paxil CR* 50 mg/day or *Paxil* 40 mg/day. The mean doses of *Paxil CR* and *Paxil* at study endpoint were 30 mg and 26 mg, respectively.

The primary efficacy parameter was the change from baseline to study endpoint on the HAM-D total score. Secondary efficacy parameters included HAM-D depressed mood item score, HAM-D anxiety factor score, HAM-D sleep disturbance score, and CGI-S score. Therapeutic response, defined as CGI-I

score of 1 (very much improved) or 2 (much improved), was assessed. In addition, remission, defined as HAM-D score ≤7, was evaluated. Quality of life was assessed with the Q-LES-Q.

In addition to showing improvements based on the HAM-D total score, patients treated with *Paxil CR* and *Paxil* demonstrated significant reductions in several additional efficacy parameters including the HAM-D depressed mood item and sleep factor item compared with placebo in the LOCF analysis. Patients treated with *Paxil CR* and *Paxil* demonstrated significant improvements compared with placebo in severity of illness as measured by the CGI-S score (LOCF; $P = 0.022$ and $P = 0.019$, respectively). Analysis at endpoint revealed that the percentage of responders, defined as a CGI-I score of 1 or 2 was significantly higher for patients treated with *Paxil CR* compared to placebo (72% vs. 52%, respectively, LOCF; $P = 0.002$). Analysis of observed cases at week 12 revealed that 86% of patients treated with *Paxil CR* reported a CGI-I score of 1 or 2 compared with 55% of patients treated with placebo ($P < 0.001$). Analysis of LOCF and OC data found that the percentage of patients treated with *Paxil CR* who experienced remission of symptoms, defined as HAM-D ≤7, was significantly higher compared with placebo, 43% vs. 26% (LOCF) and 55% vs. 29 % (OC); $P < 0.01$, respectively. At study endpoint, patients taking *Paxil CR* also demonstrated clinically relevant improvements in the Q-LES-Q.

The adverse events reported with the use of *Paxil CR* (≥5% and at least twice that for placebo) included: sweating, tremor, abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, and decreased libido (1). The percentage of patients withdrawing from the study due to adverse events were 13% for *Paxil CR*, 16% for *Paxil*, and 8% for placebo (6).

The efficacy and safety of *Paxil CR* in the treatment of MDD in the elderly has also been evaluated in a study by Pitts et al (8). A total of 525 patients with MDD were randomly assigned to 10 weeks of fixed dose *Paxil CR*. Patients that were ≥60 years of age with a diagnosis of MDD (DSM-IV criteria) and a HAM-D≥18 were randomized to received *Paxil CR* 12.5 mg/day or *Paxil CR* 25 mg/day. Patients were excluded if their primary diagnosis was any other DSM-IV Axis I disorder, they were receiving concomitant psychotropic treatment or formal psychotherapy or if they had a score ≤24 on the Mini Mental State Exam (MMSE). The primary efficacy endpoint was the mean change in HAM-D total score from baseline to study endpoint. Secondary efficacy endpoints included HAM-D depressed mood item score, HAM-D anxiety factor score, HAM-D sleep disturbance score, and CGI-S score. Response, defined as >50% reduction in HAM-D score, and remission, defined as HAM-D ≤7, were evaluated. Quality of life was assessed with the Q-LES-Q. Efficacy results are presented below in Table 1.

Table 1. Mean Change in Efficacy Parameters at Week 10 (LOCF) (8)

	***Paxil CR* 12.5 mg (*P* value vs placebo) (n = 163)**	***Paxil CR* 25 mg (*P* value vs placebo) (n = 173)**	**Placebo (n = 179)**
HAM-D Total Score*	-10.7 ($P = 0.029$)	-12.1 ($P < 0.001$)	-8.9
HAM-D Depressed Mood*	-1.46 ($P = 0.004$)	-1.63 ($P < 0.001$)	-1.1
CGI-S*	-1.5 ($P = 0.006$)	-1.6 ($P < 0.001$)	-1.1
HAM-D Anxiety*	-7.8 ($P = 0.006$)	-8.2 ($P = 0.001$)	-5.9
Q-LES-Q*	11.4 ($P = 0.001$)	11.5 ($P < 0.001$)	5.3
* $P < 0.05$ for both treatment groups versus placebo			

In addition, *Paxil CR* 25 mg also demonstrated statistical significant improvement versus placebo in HAM-D somatic score (LOCF) and HAM-D remission analysis (OC) and both *Paxil CR* 12.5 mg and

Paxil CR 25 mg demonstrated statistically significant improvements versus placebo in HAM-D Response (≥50% change from baseline at week 10; OC) and CGI Response (global improvement ≤2 at week 10; OC). However, neither *Paxil CR* 12.5 mg nor *Paxil CR* 25 mg demonstrated significant improvement versus placebo in HAM-D sleep factor (LOCF) score or overall pain assessment (LOCF).

The most common adverse events during the study occurring in ≥5% of patients and twice the rate of placebo were: somnolence, influenza, and nasopharyngitis. The percentage of patients withdrawn from the study due to adverse events were 6.1%, 8.1% and 7.3% for *Paxil CR* 12.5 mg, *Paxil CR* 25 mg, and placebo, respectively.

Fixed-Dose Trials

A randomized, 8-week, double-blind, placebo-controlled, multicenter, fixed-dosed trial evaluating *Paxil CR* 12.5 mg/day (n = 153), *Paxil CR* 25 mg/day (n = 148), and placebo (n = 146) in 447 adult patients with MDD was conducted (9, 10, 11). The primary efficacy measure was change from baseline to endpoint on the HAM-D total score. Secondary efficacy parameters included HAM-D depressed mood item score and the CGI-S score. Therapeutic response, defined as a CGI-I score of 1 or 2, and remission, defined as HAM-D ≤7, was assessed. The mean baseline HAM-D scores ranged 23.2 to 23.8.

Paxil CR 12.5 mg/day and *Paxil CR* 25 mg/day significantly reduced HAM-D total score compared with placebo ($P = 0.038$ and $P = 0.005$, respectively, LOCF). On the HAM-D depressed mood item score, *Paxil CR* 25 mg was significantly improved compared with placebo at week 8, ($P = 0.011$, LOCF). Evidence for improvement on the HAM-D depressed mood item for *Paxil CR* 12.5 mg was not statistically significant. Therapeutic response occurred in 54% of patients treated with *Paxil CR* 12.5 mg and 63% of patients treated with *Paxil CR* 25 mg compared with 51% with placebo($P = 0.035$ *Paxil CR* 25 mg vs placebo, LOCF). The remission rate was 34% for *Paxil CR* 12.5 mg, 41% for *Paxil CR* 25 mg compared with 26% for placebo ($P = 0.013$ for *Paxil CR* 25 mg vs placebo, LOCF). For the OC analysis, the remission rates were 38%, 49%, and 31% for *Paxil CR* 12.5 mg, *Paxil CR* 25 mg, and placebo, respectively ($P < 0.05$ for both *Paxil CR* doses vs placebo). The change from baseline in the CGI-S score was significantly greater for *Paxil CR* 12.5 mg and 25 mg compared to placebo ($P < 0.05$, LOCF).

Common adverse events reported with the use of *Paxil CR* (≥5% and at least twice that for placebo) included: abdominal pain, constipation, anxiety, trauma, abnormal ejaculation, sweating, female genital disorders, libido decreased, infection, and rhinitis (11). Withdrawal rates from the study due to adverse events were 5%, 1%, and 2% of patients in the *Paxil CR* 25 mg/day, *Paxil CR* 12.5 mg/day, and placebo groups, respectively.

A randomized, 6-week, double-blind, placebo-controlled, multicenter, fixed-dosed trial was conducted to compare the efficacy and safety of *Paxil CR* 12.5 mg/day (n = 94), *Paxil CR* 25 mg/day (n = 98), citalopram 20 mg/day (n = 105), and citalopram 40 mg/day (n = 97), with placebo (n = 102) in adult patients for the treatment of MDD with anxiety (12). The primary efficacy endpoint was the efficacy of *Paxil CR* 25 mg and *Paxil CR* 12.5 mg versus placebo and was measured by the proportion of Montgomery and Asberg Depression Rating Scale (MADRS) responders (defined as reduction of 50% of more in the MADRS total score from baseline) at week 6 (LOCF). The secondary efficacy endpoints included a comparison of the efficacy of 20 mg and 40 mg of citalopram versus placebo. The secondary efficacy parameters included the response based on CGI-I (score of 1 or 2) and mean change in MADRS, HAM-A, CGI-S, HAD, Sheehan Disability Scale (SDS), and the Anxiety and Depression subscales of the Hospital Anxiety and Depression Scale (HAD). This study included a citalopram treatment arm; however, the study was not designed to compare the efficacy of citalopram to *Paxil CR*.

At week 6, there was not a statistically significant difference in the proportion of MADRS responders with *Paxil CR* 25 mg (44.3%) when compared with placebo (35.6%) and the odds of being a MADRS responder with *Paxil CR* was 1.47 ($P = 0.191$, LOCF). *Paxil CR* 25 mg was associated with greater odds of response, as measured by the CGI-I (1.86, $P=0.034$ LOCF), improvements on the HAD total score (adjusted mean difference = -2.5 points; $P = 0.030$, LOCF), and improvements on the HAD Anxiety Subscales (adjusted mean difference = -1.5 points; $P = 0.016$, LOCF). No statistically significant difference was seen in these endpoints for *Paxil CR* 12.5 mg when compared with placebo. In addition, no statistically significant difference was seen with *Paxil CR* 25 mg or 12.5 mg when compared with placebo in the HAM-A total score, HAD Depression Subscale, CGI-S and SDS total score.

Treatment with citalopram 20 mg and 40 mg resulted in a higher odds ratio of being a MADRS responder compared with placebo in the LOCF dataset [1.97 ($P = 0.018$) and 1.88 ($P = 0.031$) with citalopram 20 mg and 40 mg treatment, respectively]. Statistically significant differences for citalopram 20 mg and 40 mg were also observed in the proportion of CGI-I responders, HAD total and subscale scores, and SDS total score when compared with placebo. Citalopram 40 mg demonstrated a statistically significant difference versus placebo as measured by MADRS total score and CGI-S; however this difference was not demonstrated by citalopram 20 mg. There was no evidence of statistically significant differences between either citalopram dose and placebo in the adjusted mean difference in HAM-A total score.

Common adverse events reported with the use of *Paxil CR* (≥5% and at least twice that for placebo) included: headache, dry mouth, abnormal ejaculation, diarrhea, nausea, somnolence, insomnia, asthenia, dizziness, constipation, libido decreased, abdominal pain, anxiety, dyspepsia, vasodilation, and impotence. Withdrawal rates from the study due to adverse events were 9% for *Paxil CR* 25 mg/day, 2% for *Paxil CR* 12.5 mg, and 2% for placebo.

REV0605

REFERENCES

1. Prescribing Information for *Paxil CR*.

2. Golden RN, Nemeroff CB, McSorley P, et al. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. J Clin Psychiatry 2002;63:577-584.*

3. Data on File, *Paxil CR*, BRL-029060/RSD-100N8X/1, Integrated Summary of Efficacy, December 1997.*

4. Data on File, *Paxil CR*, BRL-029060, DOF311.*

5. Rapaport M, Davies JT, Pitts CD. Efficacy of paroxetine controlled-release (CR) and immediate-release (IR) formulations in the elderly. Poster presented at US Psychiatric Congress Annual Meeting, Las Vegas, NV, Oct 28-31, 2002.*

6. Rapaport MH, Schneider LS, Dunner DL, et al. Efficacy of controlled-release paroxetine in the treatment of late-life depression. J Clin Psychiatry 2003; 64:1065-1074.*

7. Data on File, *Paxil CR*, BRL-029060/RSD-100KM9/1 Study 487. Final Clinical Report, 1-150, April 1998.*

8. Pitts CD, Schaefer DM, Lipschitz A, et al. Efficacy and tolerability of fixed, low dose paroxetine CR in the treatmetn of major depression in the elderly. Poster presented at American Psychiatric Association (APA) Annual Meeting, Atlanta, GA, May 21-26, 2005 [abstract] NR701.

9. Golden RN, Gaynes B, Pitts CD, et al. Antidepressant efficacy and tolerability of controlled-release paroxetine HCl. Presented at the 42nd annual NCDUE Meeting, June 10-13, 2002, Boca Raton, FL.*

10. Data on File, *Paxil CR*, BRL-029060/RSD-101XW5/1 Study 810. Final Clinical Report, 1-131, January 2003.*

11. Trivedi MH, Pigott TA, Perera P, et al. Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. J Clin Psychiatry 2004;65:1356-1364.*

12. Data on File, *Paxil CR*, BRL-029060/785 Study 785. Final Clinical Report, 1-92, September 2003.*

Enclosures: **Prescribing Information for *Paxil CR***
Golden RN, et al. J Clin Psychiatry 2002;63:577-584.